ESTIMATION OF EXPOSURE OF PERSONS IN CALIFORNIA TO PESTICIDE PRODUCTS THAT CONTAIN CYROMAZINE

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ABSTRACT

The Ciba Geigy Corporation has applied for a Section 3 registration to apply cyromazine formulated as Larvadex® 2 SL to chicken manure to control flies. The risk characterization document prepared by the Medical Toxicology Branch of the California Department of Pesticide Regulation for cyromazine indicates the active ingredient has the potential to cause "developmental effects" in laboratory animals. Dermal absorption of a 10 µg/cm² dose is estimated to be 17%. Animal feeding studies have identified the primary metabolites of cyromazine as hydroxycyromazine, melamine, and methylcyromazine with approximately 70% of the radioactivity excreted as unmetabolized cyromazine. Absorbed cyromazine is rapidly excreted, primarily in the urine, with the majority of the dose being eliminated within 24 hours. Dermal and inhalation exposure to cyromazine from applying Larvadex® 2 SL in a chicken house ranged from 0.40-16.77 mg per workday depending on the application method used. Environmental monitoring indicated that unprotected persons entering a chicken house immediately after an application will not be exposed to significant levels of cyromazine.

This report was prepared as an Appendix B to the Department's Risk Characterization Document for cyromazine.

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* David Haskell was the lead person for the preparation of this document.

APPENDIX B

California Department of Pesticide Regulation
Worker Health and Safety Branch
Human Exposure Assessment

CYROMAZINE

February 19, 1993

PHYSICAL AND CHEMICAL PROPERTIES

Cyromazine [N-cyclopropyl-1,3,5-triazine-2,4,6-triamine, CAS Registry Number 66215-27-8, molecular formula $C_6H_{10}N_6$, molecular weight 166.19] is an insecticide of the triazine family. This triazine member has been used primarily as an insect growth regulator to control dipterous (e.g., fly) larvae on animals and to control leafminers in ornamentals and vegetables. The compound has a vapor pressure of $<1x10^{-6}$ mm Hg (< 0.13 mPa) at 20^{o}C, with a specific gravity of 1.35 g/ml and a melting point of 220 – 222^{o}C. Cyromazine is moderately soluble in water (11 g/L at 200^{o}C and pH 7.5) and only slightly soluble in methanol. The compound, which is commercially available as a colorless crystal and is stable at <310^{o}C, has been observed to withstand hydrolysis for 28 days at up to 700^{o}C (Royal Society of Chemistry, 1990: Worthing and Hance, 1991).

FORMULATION

Cyromazine was first synthesized by Ciba-Geigy in 1980 and has since been registered to the company under several trade names (Neporex®, Vetrazine®, Trigard®, Armor®, CGA 726620, and Larvadex®) for various veterinary and plant protection uses. The cyromazine product currently under review by the Department of Pesticide Regulation (DPR) is Larvadex® 2SL. As a soluble concentrate, each gallon of Larvadex® 2SL contains 0.17 lb of cyromazine (2% of the product) as the active ingredient (ai). The maximum label rate is 1 gallon of 0.1% finished spray per 100 sq. ft. of surface area of manure or other sites where maggots are active. The label specifies that Larvadex® 2SL shall not be sprayed more frequently than once every 21 days at a particular site.

Some background information is necessary to understand how this product will be used under California conditions. The current Larvadex® label limits the use of cyromazine to fly control around chicken layer and breeder operations only. Based on information provided by farm advisors, poultry operators, and staff from the Agricultural Commissioners' offices, cyromazine will probably be used primarily by that segment of the poultry industry involved in egg production. The egg industry utilizes layer chickens that are kept in wire cages and maintained in large houses where their numbers are in the thousands. The manure accumulates on the concrete floor underneath the cages and is removed periodically. How often the removal takes place and the ability to control its moisture content are the principle factors in managing fly problems. Most operations practice some form of integrated pest management centered around sanitary practices to control fly infestations by the systematic removal and drying of the manure. Or the manure can be removed in a slurry and retained in ponds to retain a high level of moisture to control fly propagation.

These practices include the management of fly predators and parasites and the judicious use of pesticides. Only a few products are currently registered for use inside the chicken houses to control adult flies that roost on the inside walls.

Flies are not a year round problem in California. In the San Joaquin Valley, the propagation season lasts from late March into October (Bokhai, 1993). The first frost usually occurs by mid-November and the flies over-winter as pupae until March. In the inland valleys of San Bernardino and Riverside Counties where the egg laying industry is located, the fly season starts in May and continues into November (McKeen, 1993a). Mitch Bernstein (1993) of San Bernardino Vector Control estimated the fly season can start in early spring and go into October. The average fly season was calculated to last for 210 days.

Two species of flies are of major concern for poultry operations in California (McKeen, 1984). The Lessor Housefly, Vania canicularis, is predominately a cool season pest during the early spring and fall months (McKeen, 1993a; Bokhai, 1993**).** It has the habit of not roosting readily and its constant flying can be very irritating. During the warmer summer months, the Common Housefly, Musca domestica, becomes the dominate species (McKeen, 1993; Bokhai, 1993). Unseasonable rains or broken water pipes that prevent the timely drying and removal of manure can cause sudden fly infestations of both species.

Most poultry operations also maintain their own breeding flocks which provide eggs for hatching into laying hens or baby chicks to raise into broilers. As a rule their numbers usually represent about 1% of the broiler or laying population of the ranch (Bokhai, 1993). These flocks are maintained in similar houses as the layers and can experience the same fly problems.

REGISTRATION STATUS

Larvadex® is currently registered by the U. S. Environmental Protection Agency for use as a feed supplement or a directed spray to control developing fly larvae. The registrant has applied for a Section 3 registration of the directed spray formulation (Larvadex® 2SL) in California.

USAGE

The active ingredient cyromazine currently is not registered for use as a pesticide in California. Consequently, data are not available on the usage of cyromazine in California. However, projected sales by the Ciba Geigy Corporation for the California market are estimated at 6,000 gallons annually or about 1,020 lbs of a.i.

LABEL PRECAUTIONS

Larvadex® 2SL is labeled as a Toxicity Category III pesticide. Initially, the Larvadex® 2SL label did not specify any protective clothing to be worn when handling cyromazine. However, the proposed California label requires applicators to wear a long-sleeved shirt and long pants, boots, rubber gloves and a dust mask. California regulations require some form of eye protection to be worn when applying this pesticide by the methods listed on the label. The label advises users to avoid contact with eyes, skin, or clothing and not to breathe vapors or spray mist. Contact with eyes will cause moderate eye irritation. Should contamination occur, the label directs the user to wash the exposed skin with soap and water, and to flush the eyes with plenty of water. If exposure occurs via inhalation, handlers shall move or be removed to fresh

air. The user is required to seek medical attention if irritation from exposure to cyromazine develops or persists. The label prohibits the direct application of this product to poultry or poultry feed or the feeding of manure treated with Larvadex® to animals. The label advises that a lapse of 24 hours be allowed between the last application and slaughter to avoid illegal residues.

WORKER ILLNESSES

Since cyromazine has not been registered for use in California, illnesses have not been reported from its use.

DERMAL HYPERSENSITIVITY

One dermal sensitization study was submitted in support of the registration of cyromazine in California. The test was conducted under the (commonly accepted) assumption that acute toxicity of the new Larvadex® formulation with 2% cyromazine be considered equal to the results from using the old formulation (under the trade name of Trigard®) that contains 5% cyromazine. According to the new product label, the only change in the new formulation is a reduction in the active ingredient content by the addition of water.

The study investigated the potential of cyromazine to cause delayed dermal sensitization after repeated exposures (Sabol, 1983). The backs of 10 male Hartley albino guinea pigs were shaved and treated with 0.5 ml of Trigard® 5%. The test material was left in contact with their skin for approximately 6 hours. A total of 11 treatments were made in 35 days. Observations for skin reactions were made at approximately 24 hours after each application. In this study, dinitrochlorobenzene (DNCB) at 0.05% (w/v) in ethanol was applied to ten other guinea pigs in a similar manner, as the positive control. As expected, a sensitizing reaction was observed in the animals treated with DNCB. No skin reaction was observed, however, among the test animals following treatment with Trigard® 5%. The average skin reaction score for this test group for their virgin site was 0.2, out of a possible 8.0. Consequently, Trigard® 5% (as well as Larvadex® 2SL) was not considered to be a dermal sensitizer in guinea pigs.

DERMAL AND INHALATION ABSORPTION

Two dermal absorption studies were conducted with ^{14}C-cyromazine applied to the shaved backs of male rats. The first study observed the rates of absorption using three dose levels: 0.1, 1.0, and 100 mg per rat equivalent to 10, 100, and 10,000 µg/cm², respectively (Murphy and Simoneoux, 1985). The animals were exposed for 1, 2, 4, and 10 hours and then sacrificed. The percents of dose recovered in the treated skin were: 29-35% for low dose, 19-27% for mid dose, and 8-15% for high dose. The rates of dermal absorption, calculated as the percent of the dose recovered in urine, feces, carcass, plasma, and RBC were 4.5-11%, 3.5-11.4%, and 2.2-7.1 % for low, mid and high doses, respectively. Because of the short sample collection periods and the high amount of bound skin residues, this study was not considered for the determination of dermal absorption.

A second study was conducted using three dose levels: 0.1, 1.0, and 10 mg/rat equivalent to 0.01, 0.1, and 1 mg/cm², respectively (Murphy, 1987). Labeled cyromazine (low and mid doses) and labeled cyromazine plus non-labeled cyromazine (high dose) were mixed with the formulation blank prior to application to the shaved skin sites of the male rats.

Four rats were used for each sacrifice time. The treated skin was covered with a nonocclusive protective appliance. At the conclusion of the exposure, the treated skin was washed with a 2% Dove solution in water. There were two distinct observation periods. For the short-term sample collection, the animals were exposed for 2, 4, and 10 hours and then sacrificed. With the long-term study, the exposure times were 10 and 24 hours and the animals were sacrificed 48 hours after the exposure. Samples collected for the analyses included blood, carcass, skin washes, cage washes, treated skin and the skin around the treated area, urine, feces, and rinses of the protective appliance.

The results indicate that cyromazine is rapidly absorbed into the skin and saturated in a short period of time. The percent of the dose absorbed or recovered from the treated skin was similar for all dose levels. Bound skin residues, total dose recovery and dose absorbed are shown in Table 1.

Dermal absorption of cyromazine is apparently time and dose dependent; the absorption rate for the low dose is greater than the higher doses. Also, the percent of dose absorbed is greater with the longer exposure time. At the end of the longest exposure time (72 hours), the amount of bound skin residues as percent of dose for low, mid and high doses were 7.2, 11.5 and 5.9 percent (Table 1), respectively. There is an obvious pattern that bound skin residues are decreasing with increasing sacrifice time. For example, bound skin residues are 22.6 and 7.2 percent for the sacrifice time 2 and 72 hours, respectively (Table 1). A similar pattern is also observed for the excretion of the dose in urine and feces (Table 2). It is unjustifiable to add the percent bound skin residues directly to percent dose absorbed, because it is unlikely that all bound residues will be further absorbed and excreted. Furthermore, there are adequate data to estimate graphically the bioavailability or the amount of bound residues that is available for further absorption and excretion. Cumulative excretion data for any given compound always approaches a maximum upper bound. An asymptotic plot of the percent dose recovered in the excreta for 24, 48 and 72 hour collection times (Table 2) was based upon the exponential saturation equation described by Spain (1982). An example of the plot and output (performed by Steve Saiz, Worker Health and Safety Branch) is shown in Figure 1 and attachment 1. The bioavailability of skin residues is the difference of the percent of dose at asymptote and at the termination of the study. The percent of dose that are bioavailable from bound skin residues are then added to the percent of dose absorbed in 72-hour sacrifice time (Table 3).

This observation is supported by the rate of excretion of the low dose in urine. From 48 to 72 hours, 1.54% of the dose was excreted in urine. Between 24 and 72 hours, the percent of the dose excreted decreases by approximately 50% every 24 hours. If this rate of excretion continues for three more days, an additional 1.35% of the dose will be excreted in urine. This amount is almost equivalent to the percent of the dose (1.24%) estimated to be available by asymptotic extrapolation.

Table 1. Percent of administered dose absorbed or retained in treated skin.

	Exposure time (hours)				Exposure time (hours)	
	2	4	10	24	10	24
Sacrifice time (hours)[a]	2	4	10	24	58	72
Low dose (0.01 mg/cm²)						
Total recovery	100.8	88.7	95.5	92.2	110.4	101.6
Skin residues	22.6	19.0	18.6	23.9	14.8	7.2
% Dose absorbed[b]	3.3	7.3	7.6	6.9	20.3[c]	16.1
Mid dose (0.1 mg/cm²)						
Total recovery	100.4	102.3	97.9	99.1	102.0	103.3
Skin residues	9.9	13.6	12.0	21.3	8.4	11.5
% Dose absorbed[b]	6.6	3.5	5.1	2.8	8.8	12.5
High dose (1.0 mg/cm^2)						
Total recovery	87.3	77.5	76.8	89.0	94.9	101.1
Skin residues	4.5	6.3	8.6	9.3	3.2	5.9
% Dose absorbed[b]	2.1	0.8	0.8	2.6	11.6	9.1

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[a] Hours after treatment
[b] Percent dose in blood, urine, feces, carcass, and cage washes.
[c] Cage washes for rat # 3816 was not included due to abnormally high values compared to other animals.

Table 2. Percent administered dose excreted in urine and feces following 10- and 24-hour exposures.

		Sample collection time (hours)		
		10	34	58
Dosages for 1 0-hour exposure				
0.01 mg/cm²	Urine (non-cum.)	2.48	4.26	2.27
	Feces (non-cum.)	0.07	0.11	0.24
	Urine + feces (cum.)	2.55	6.92	9.43
0.1 mg/cm²	Urine (non-cum.)	2.66	1.99	2.39
	Feces (non-cum.)	0.23	0.05	0.08
	Urine + feces (cum.)	2.89	4.93	7.44
1.0 mg/cm²	Urine (non-cum.)	3.16	2.33	0.66
	Feces (non-cum.)	0.01	0.08	0.05
	Urine + feces (cum.)	3.17	5.58	6.29
		Sample collection time (hours)		
		24	48	72
Dosages for 24-hour exposure				
0.01 mg/cm²	Urine (non-cum.)	5.64	3.53	1.54
	Feces (non-cum.)	0.16	0.13	0.11
	Urine + feces (cum.)	5.8	9.46	11.11
0.1 mg/cm²	Urine (non-cum.)	3.31	3.37	1.96
	Feces (non-cum.)	0.09	0.08	0.08
	Urine + feces (cum.)	3.40	6.85	8.90
1.0 mg/cm²	Urine (non-cum.)	0.45	4.37	1.78
	Feces (non-cum.)	0.01	0.22	0.09
	Urine + feces (cum.)	0.46	5.05	6.92

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(cum. = cumulative)

Table 3. Dermal absorption of cyromazine in rats when bound skin residues were taken into consideration.

		Exposure time (hours)	
		10	24
	Sacrifice time (hours)	58	72
0.01 mg/cm²	% Dose absorbed	20.30	16.10
	% Dose bioavailable[a]	4.42	1.24
	• Dermal absorption	24.72	17.34
	• Dermal absorption[b]	22.39	17.07
0.1 mg/cm²	% Dose absorbed	8.80	12.50
	% Dose bioavailable[a]	1.14	2.94
	• Dermal absorption	9.94	15.44
	• Dermal absorption[b]	9.75	14.95
1.0 mg/cm²	% Dose absorbed	11.60	9.10
	• Dose bioavailable[a]	0.30	1.28
	• Dermal absorption	11.90	10.38
	• Dermal absorption[b]	12.54	10.37

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a. From asymptotic extrapolation (% dose at asymptote minus % dose excreted in the last sample collected).
b. Corrected percent dermal absorption for total dose recovery.

The low dose in this rat dermal absorption study most closely approximates the estimated human dermal dose. At the exposure rate of 0.01 mg/cm² a 76-kg man with a body surface area of 19,400 cm² (50-percentile man) would experience approximately 194 mg of dermal exposure (U.S. EPA, 1985). The highest exposure rate observed in the exposure studies was 17 mg/day for the backpack sprayer.

Dermal absorption of the three dose groups for the 58-hour sacrifice time (Table 3) appeared atypical because the mid dose showed the lowest absorption. Linear plots of the percent

dermal absorption at 58 hours versus dose levels gave a dermal absorption of 16.6% for the low dose with a low coefficient of determination. This percent absorption was similar to the dermal absorption of low dose for the 72-hour sacrifice time (17.3%). The plots of percent dermal absorption and doses for the 72-hour sacrifice time gave a high coefficient of determination ($R^2 = 0.941$). Considering the results obtained from these two sacrifice times, a dermal absorption of 17% was used for worker exposure estimates. This rate is used under the assumption that the dermal dose from occupational exposure to cyromazine is not more than 50 µg/cm². If this is not the case, dermal absorption will be determined from a curve constructed from plotting the percent dermal absorption and dose levels for the 72-hour sacrifice time.

Inhalation absorption data was not available for this chemical in animals. Inhalation absorption was based on the study of several chemicals in humans by Raabe (1988). His study indicates that vapor uptake is proportional to the inverse square root of the molecular weight. The relationship was found for pure vapor in air for several compounds in humans. He observed that chemicals in the form of vapors were retained about 50% in the lungs. These residues were held by the alveoli and then 100% absorbed. A 50% inhalation uptake and 100% absorption was used for the worker exposure estimates.

ANIMAL METABOLISM

Two animal metabolism studies were conducted by the registrant to support the registration of Larvadex®. Rats were used in both studies to investigate the biologic fate of cyromazine. The first study conducted in 1978, was reviewed by DPR in 1987 and 1988, and found to be incomplete (and not upgradeable) because of too few animals employed per dose group (Simoneaux and Cassidy, 1978).

The second, more recent study was determined to be acceptable, since it was conducted in compliance with the data requirements set for pesticide registration (Capps, 1990). A total of 39 Charles River rats in four dose groups were used in the second study. Three of the four groups, consisting of 5 males and 5 females each, were given single or multiple oral (intragastric) doses of 300 mg/kg or 3 mg/kg (vehicle: Hi Sil 233/1% aqueous carboxymethylcellulose). In the high and the low oral dose groups, the animals were given only a single dose of ring labeled ^{14}C-cyromazine (with purity > 96%). The third oral dose group was treated daily for 14 days with unlabeled cyromazine at 3 mg/kg, and then with a *single* radiolabeled dose of 3 mg/kg on Day 15. In addition, 5 other male and 4 other female rats were given a single intravenous (IV) dose of ^{14}C-Cyromazine (vehicle: deionized water). In all cases, the test animals were monitored over a 7-day period for recovery of radioactivity in the urine, feces, and tissues against time.

The total radioactivity eliminated via urine and feces was >85% for all four dose groups, with more than 80% of the radioactivity excreted in the urine alone. Regardless of the dose route, the majority of administered radioactivity was eliminated in the urine during the first 24 hours after dosing. The amount of radioactivity eliminated in the feces for the four groups was between 3% and 7% of the total administered radioactivity. Recovery of the radioactivity in the tissues ranged from non-detectable to 0.01 ppm for all test animals except the high oral dose group. The carcass residues in the high dose group averaged 0.67 ppm, with approximately 80% obtained from the liver and 20% from red blood cells. When the radioactivity detected in the carcass was expressed as a percentage of the dose, the values for all dosage groups was <0.37% of the dose.

The major metabolites present in the urine and fecal extracts were characterized by either high-performance liquid chromatography or thin-layer chromatography. The metabolite distribution in both extracts was shown to be similar, with approximately 70% of the radioactivity associated with unmetabolized cyromazine. The quantifiable secondary metabolites found in the urine and feces were hydroxycyromazine, melamine, and methylcyromazine. None of these three, individually, accounted for more than 9% of the radiolabeled dose in either excretion. The metabolism data presented in the study suggest that cyromazine is metabolized to hydroxycyromazine, methylcyromazine, and melamine. Additional products, which each accounted for <1 % of the administered radioactivity, were believed to be metabolized directly from hydroxycyromazine and methylcyromazine.

OCCUPATIONAL EXPOSURE

I. Applicator Exposure

A study of Larvadex® 2SL was conducted in 1988 to observe the occupational exposure from applying cyromazine in a poultry house (Merricks, 1988). Since poultry operations employ many different techniques to apply pesticides, the study included a survey of owners and managers of poultry businesses to determine the prevalent methods. Two of the application methods observed in the study, the backpack sprayer and the portable power sprayer, were among the most common methods used to apply pesticides. Of the 216 poultry businesses surveyed, 42% and 32%, reported using, respectively, the portable sprayer on wheels and the backpack sprayer to apply insecticides in and around their poultry houses. Also, 40% of the businesses reported using the hand-held fogger. However this method of application is not permitted by the Larvadex® 2SL label. Other reported methods used to apply insecticides including the hand-held sprayer, accounted for less the 9% of the businesses reporting in the survey.

The protocol called for four poultry operations located in Maryland, Pennsylvania and Virginia to participate in the study. The size of their operations ranged from 9,500 birds (45' X 100' house) to 120,000 birds (58' X 500' house). Larvadex® 2SL was applied as a 0.1% solution to the piles of manure underneath the cages to control developing fly larvae. Each worker, operating the hand-held or backpack sprayers, mixed and applied a two-gallon mixture of cyromazine three times for each replicate. This entailed the handling of 0.024 kg of a.i. per replicate. Two persons, one to mix and load the spray material and the other to spray with a 200' hose, were used to operate the portable power sprayer. Each replicate consisted of mixing one gallon (0.077 kg a.i.) of Larvadex® with 19 gallons of water and treating the manure to the point of near run-off. A total of sixteen replications of mixing and applying Larvadex® were conducted for each application method at four different sites. However, it was later decided by EPA and Ciba Geigy that analysis of the samples from nine replicates at three different sites was adequate for the study.

The study was designed to estimate the potential and actual exposure from an application of Larvadex® with workers wearing a dust mask and rubber gloves in addition to work clothing (shoes, socks, long pants and long sleeved-shirt). Dermal exposure was detected with two sets of patches made of alpha-cellulose attached to a plastic frame with an aluminum foil backing. One set of patches was covered with cloth to represent the protective clothing worn by the applicators. Both types of patches were attached side by side to the outside of the Tyvek® coveralls at various body locations. Exposure to the hands was detected with cotton gloves worn underneath the latex gloves.

Respiratory exposure was monitored during the exposure period with a personal air pump equipped with a tee to draw air through two filters. The air pump was calibrated to draw air through the two filters at a rate of two liters per minute. The polyurethane foam in the filters was covered with dust mask material to simulate the dusk mask requirement on the label. Cyromazine has a vapor pressure of $<1x10^{-6}$ mm Hg at $20^{o}C$. At this moderately low vapor pressure, a large number of fine particles are not expected from volatilization. Most spray particles were expected to be >50 µ and will be trapped in the dust mask material.

Quality control procedures were conducted at the application site and in the laboratory. All sample media were spiked in the field at various rates and frozen to serve as positive controls. Additional media samples were spiked prior to the exposure period to determine the stability of cyromazine in samples exposed to the poultry house environment. Samples were taken from each tank mix for all the sprayer types. A freezer storage stability study was initiated in the laboratory for all the sample media. The alpha-cellulose patches, cotton gloves samples and foam filters were extracted with hydrochloric acid, reacted with cation exchange resin, washed, eluded and then subjected to liquid chromatographic analysis.

The results indicate that cyromazine is relatively stable during storage. An average of 85% of the initial spikes was recovered from the field-fortified patches, 79% from the gloves and 84% from the foam filters. These rates of recovery were confirmed by results from the laboratory freezer study. All the dermal and inhalation exposure calculations were adjusted for the minor losses that occurred in storage.

The minimum detectable level (MDL) for cyromazine on the patches was 0.001 µg/cm² and 0.2 µg total for the gloves and the foam filters. Cyromazine residues were not detected on any of the foam filters taken from the personal air sampling pumps. In accordance with the exposure guidelines listed in Subdivision U, Applicator Exposure Monitoring, (U.S. EPA, 1987), one-half the limit of detection was used to make the exposure calculations when residues were not detected for a particular sample. The following levels, representing 1/2 the MDL for the foam filter samples, were used to calculate the inhalation exposure for the various work tasks; 0.001 µg/L-backpack sprayer, 0.001 µg/L-handheld sprayer, 0.005 µg/L-power sprayer mixer/loader and 0.002 µg/L-power sprayer applicator (Merricks, 1988). To keep the inhalation exposure equivalent for each of the work tasks, the MDL's vary because the amounts of a.i. handled during the replicates are different for each work task and the exposure times differ for each work task.

Inhalation exposure was derived as the mg of exposure per kg of a.i. handled for each replicate. The inhalation exposures listed in the tables of the study represent the mean values from the nine replications of each work task and were calculated using this formula:

$$\frac{\text{(level of residue in sample) (29 L/min, (U.S. EPA, 1987)) (time of replicate in min)}}{\text{(kg of a.i. handled) (percent recovery of field spikes) (1,000 µg/mg)}}$$

Example calculation for hand-held sprayer: 0.001 µg/l X 29 L/min X 53 min./ 0.024 kg per replicate X 0.84 X 1,000 µg/mg = 0.076 mg of inhalation exposure per kg of a.i. handled.

Exposure to the body was calculated as the total exposure per 18,980 cm² of surface area excluding the hands. When the surface area of the hands (840² are included, this value is 102% of the 19,400² body surface area (50 percentile man) used to estimate the surface area of a 76 kg man (U.S. EPA, 1985). The exposure values from the study are listed in Table 4 without any correction for surface area.

Workers operating the hand-held sprayer had residues below detectable levels with the exception of unprotected patches located on the ankles and thighs. These patches had residues consistently above the limit of detection. The backpack operators received the highest dermal exposures of all the workers, with the ankles, thighs, shoulders and back patches detecting the greatest residues. All the protected patches for the mixer/loaders loading the portable power sprayers had residues below the detection limits with the exception of one. Most workers applying cyromazine with the portable power sprayer had detectable residues on the thighs, ankles and forearms.

Residues detected on the cotton gloves worn underneath the chemical resistant rubber gloves were considered as actual exposure to the hands. The residues present on the cotton gloves were undetectable for eight workers and in the range of 0.20 to 0.42 mg for three other workers (two backpack applicators and one portable sprayer mixer, loader). The 4.25 mg of residue detected on the hands of a portable sprayer applicator was probably the result of an accidental spill.

Occupational exposure to cyromazine was expressed in terms of milligrams of exposure per kilogram of active ingredient handled per replicate in Tables 18-21 of the study. The mg of exposure per kg of a.i. handled per replicate was calculated as the average from the nine replicates for each sprayer type and job function. However, to identify the dermal and inhalation exposures, the values in the following table were listed as the actual exposure per replicate. These were calculated by multiplying the dermal and inhalation exposure values by the number of kg of a.i. handled during the replicate. This value was then multiplied by the number of replicates that can be completed in an eight-hour workday in order to estimate the Daily Dermal and Inhalation Exposures. Example for the hand-held sprayer: (1.442 mg of dermal exposure/kg of a.i. handled/replicate) X (0.024 kg of a.i. handled) X (9 replicates per 8-hour workday) = 0.31 mg of Daily Dermal Exposure and (0.072 mg of exposure/kg of a.i. handled/replicate) X (0.024 kg of a.i. handled) X (9 replicates per 8-hour workday) = 0.016 mg of Daily Inhalation Exposure.

Table 4. Mean Daily Exposure to Workers Applying Cyromazine with Various Types of Sprayers[a].

Application Method	Dermal Exposure mg/replicate	Inhalation Exposure mg/replicate	Number of Replicates per/8-hr day	Daily Dermal Exposure mg/person/8-hr day	Daily Inhalation Exposure mg/person/8-hr day
Handheld Sprayer	0.035	0.0017	9.0	0.31	0.016
Backpack Sprayer	1.67	0.0017	10.0	16.7	0.017
Power Sprayer					
mixer/loader	0.012	0.0018	14.0	0.17	0.025
applicator	0.27	0.0018	14.0	3.8	0.025

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[a] Workers were wearing shoes, socks, long pants, long sleeved-shirt, dust mask and rubber gloves.

Since male workers predominate in agriculture, the exposure assessment was conducted to assess male exposure to cyromazine. Occupational exposure was estimated based on a body weight of 76 kg and a body surface area of 19,400 cm^2 for the 50th percentile man (U.S. EPA, 1985). The ratio of body surface area to body weight is 255 cm^2/kg (19,400 cm^2/76 kg). This ratio for the 50th percentile women is 273 cm^2/kg based on a body surface area of 16,900 cm^2 and a body weight of 62 kg. These surface to body weight ratios are fairly constant between males and females. Although female exposure to cyromazine was not quantified in the occupational exposure assessment, the exposure estimates for the male workers are representative for female workers.

Exposure to cyromazine will be limited to the workers and owners of the poultry ranch. Owners of poultry operations in California generally do not engage the services of a pest control operator (PCO) to assist them in their pest control activities (Bokhai, 1993; Bell, 1993). Since chickens are raised in enclosed habitats, they are very susceptible to various avian diseases (University of California, 1977). Operators are concerned with protecting their flocks from Infectious Coryza, New Castle disease, bronchitis, fowl pox and other avian diseases (McKeen, 1993a). An infection in one bird threatens the whole flock. Sanitary measures for people and equipment entering the chicken houses, particularly where the young birds are kept, are important control measures for these infectious diseases (University of California, 1977). Farm advisors make it a practice to visit only one operation per day. Operations may require non company personnel to wear disposable protective clothing upon entering the houses to prevent the spread of infectious diseases (Post, 1993). Because of this desire to isolate each ranch's birds, even from other birds within the same company, each ranch manager is provided with their own spray equipment to make all the necessary pesticide applications (Maust, 1993).

Utilizing the services of a PCO would incur the risk that diseases could be transmitted from one operation to another via infected spray equipment and personnel. An analysis of the pesticide use reports now available under the 100% pesticide use reporting regulations demonstrate this is indeed the case. Riverside County is the leading egg producing county in California (California Agricultural Statistics Service, 1992). A member of the Riverside County Agricultural Commissioner's staff conducted a search for pesticides reported used by PCOs for applications to poultry operations (Riverside Ag. Commissioner, 1993). The search indicated 211 pesticide applications were reported at poultry sites for January-June 1992. All applications were made by the owners or operators of the poultry ranches.

The farm advisor for San Bernardino County (McKeen, 1993b) and the extension poultry specialist at the University of California, Riverside (Bell, 1993) estimate that treatments will be made on problem ranches only on an emergency basis. These ranches are usually located in rural areas that are rapidly urbanizing with residential neighbors that have a low tolerance for flies. The Yucaipa poultry district in San Bernardino County has experienced chronic fly problems even with good integrated pest management. This district has six companies with approximately 1.2 million birds located on 13 ranches (Bernstein, 1993). A typical poultry house (40' by 400') with three hens per cage contains approximately 13,230 birds (McKeen, 1993b). These 1.2 million birds are estimated to be located in 90 houses on 13 ranches with an average of 7.5 houses per ranch. Mr. Maust (1993) operates a 175,000 layer business with 110,000 birds located at the "Home" ranch in 17 houses. Utilizing a motorized spray cart with a 50 gallon tank, he indicated it would take about 20 minutes to spray each house and that the whole ranch could be sprayed in one day. Using this profile as typical for the Yucaipa district, a cyromazine treatment of all the chicken houses on one ranch could be completed in one day. Assuming each ranch manager will make all the applications for their ranch, a maximum treatment program with applications of Larvadex® made every 21 days during the fly season will result in ten exposure days per year.

Table 5. Estimation of Lifetime Average Daily Dosage for Applicators of Cyromazine.

Application Method	Absorbed Daily Dosage[a] µg/kg/day	Average Annual Daily Dosage[b] µg/kg/day	Lifetime Average Daily Dosage[c] µg/kg/day
Handheld Sprayer	1.2	0.03	0.02
Backpack Sprayer	37.8	1.04	0.60
Power Sprayer			
mixer/loader	0.60	0.02	0.01
applicator	8.65	0.24	0.14

Haskell, WH&S, 1991

a. Since the estimated rates of dermal exposure are less than 10 µg/cm² the rate of dermal absorption was 17% (Murphy, 1987). Inhalation absorption is considered as 50% uptake and 100% absorption (Raabe, 1988). Weight of worker was 76 kg.

b. Assumes a maximum of ten applications made per year with the operator completing each application in one day. In California, the large size of most poultry operations dictates that some motorized form of the power sprayer would be the most likely method of application. One person would probably perform both the mixing/loading and application work tasks. Exposure for this worker would be the sum of the exposures for the power sprayer mixer/loader and applicator. The hand-held and backpack sprayers would likely be used for spot treatments only.

c. Assumes 40 years of exposure from application of cyromazine over a 70 year lifespan.

II. Field Worker Exposure

The volatilization of residual cyromazine after the application was monitored with alpha cellulose cards and personal air sampling pumps fitted with foam filters. The cards were placed on the floors and walls of the treated houses. Additional cards and the air pump samplers were placed in the aisles at a height of five feet to collect residues in the breathing zone. The cards and foam filters from the pumps were collected immediately after the application and at 1, 2 and 4 days post application. Cyromazine residues were not detected (<0.001 µg/cm² for wall cards and <0.08µg/cm² for foam filters) on any of the air pump filters or cards attached to the walls of the poultry houses. Only trace amounts of residues (<0.001-0.005 µg/cm²) were detected on the cards placed on the floor of one house. These results indicate that unprotected workers entering a poultry house after an application of Larvadex® 2SL will not be exposed significantly.

According to the label, manure treated with Larvadex® 2SL can be used as a soil fertilizer supplement. For manure treated solely with Larvadex® 2SL, the maximum allowable rate is 4 tons per acre per year. In addition, the label cautions against applying manure treated with Larvadex® 2SL to small grain crops that will be harvested or grazed, as illegal residues may result. Degradation data indicate that the levels of cyromazine in treated chicken manure remain stable 21 days after application (Honeycutt, 1982). Two hundred chickens will excrete

approximately 66 lbs of manure per day with a manure surface area of 100 square feet (Bell, 1993). The levels of cyromazine present, 21 days after a treatment of 0.0086 lb. of a.i., are estimated to be 6.2 ppm. Due to the obnoxious nature of chicken manure, workers removing and spreading it are expected to wear a minimum of shoes, socks, long pants and long-sleeved shirt. If they were exposed dermally to 100 grams of treated chicken manure from working an eight-hour day, the exposure to cyromazine would be equivalent to 0.62 mg. The absorbed dose for a 76-kg man would be only 1.4 µg/kg. This level of exposure for workers loading and spreading treated manure is not expected to be significant.

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ATTACMENT 1

Determination of bioavailability of bound skin residues.
(Cyromazine: 10 µg/cm²; 24-hour exposure with 72-hour sacrifice times)

ITERATION	LOSS	PARAMETER VALUES		
0	.23924100+02	.12000+02	10000+00	.60000+01
I	.49592260+01	.11150+02	.96170-01	.17110+02
2	.57545500+00	.11070+02	.64520-01	.13670+02
3	.27283560+00	.11140+02	.57730-01	.11640+02
4	.99132260-01	.11520+02	.47630-01	.98410+01
5	.53490850-01	.11720+02	.43520-01	.84740+01
6	.97926970-02	.12170+02.	.36850-01	.63420+01
7	.61282110-03	.12310+02	.34930-01	.57870+01
8	.461908I0-04	.12340+02	.34780-01	.57370+01
9	.66342400-05	.12340+02	.34740-01	.57390+01
10	.32405680-06	.12350+02	.34670-01	.57080+01
11	.49191590-08	.12350+02	.34670-01	.57090+01
12	.24687370-09	.12350+02	.34670-01	.57090+01
13	.76112290-11	.12350+02	.34670-01	.57090+01

DEPENDENT VARIABLE IS: % Dose excreted = 5.8, 9.5, and 11.1 for 24, 43, and 72 hours after treatment, respectively.

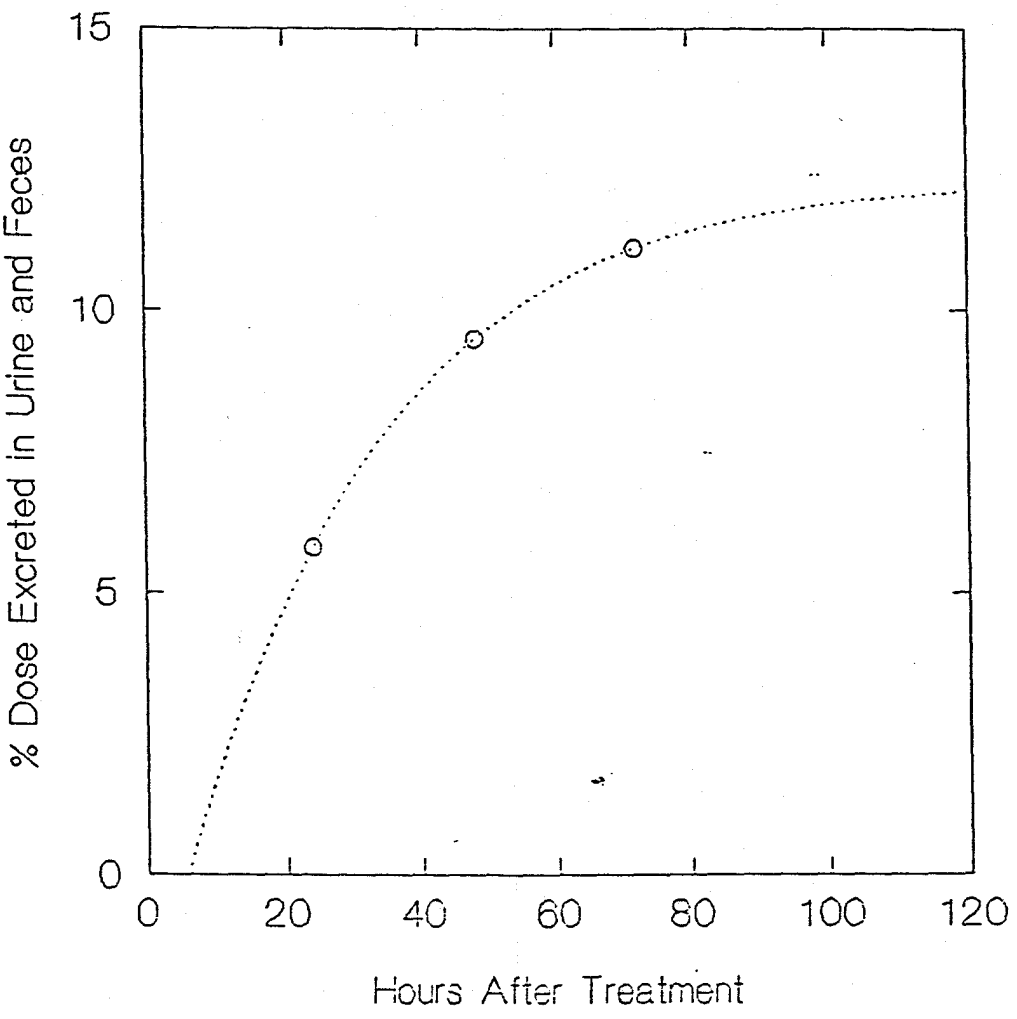
PARAMETER	ESTIMATE
A	12.3502
B	0.0347
C	5.7087

Bioavailability of bound skin residues = 12.35-11.11 = 1.24%

FIGURE I

Determination of Bioavailability of Bound Skin Residues
(Cyromazine: 10 µg/cm²; 24 hour exposure; 72 hour sacrifice time)

Y= 12.35*(1-EXP(-0.0347*(X-5.709)))



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